Journal of Surgical Oncology

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Journal of SURGICAL ONCOLOGY

REVIEW ARTICLE OPEN ACCESS

Review of 2022 PSOGI/RENAPE Consensus on HIPEC

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Received: 21 August 2024 | **Accepted:** 26 August 2024

Keywords: consensus | HIPEC regimens | hyperthermic intraperitoneal chemotherapy | peritoneal surface malignancies

ABSTRACT

The 2022 PSOGI (Peritoneal Surface Oncology Group International) and RENAPE (French Network for Rare Peritoneal Malignancies) consensus on hyperthermic intraperitoneal chemotherapy (HIPEC) was a comprehensive effort aimed at standardizing treatment protocols for various peritoneal malignancies. This initiative is critical due to the wide range of technical variations in HIPEC procedures and the resulting need for standardization to ensure consistent and effective patient care and meaningful audit of multicenter data.

1 | Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a complex treatment modality that is still hampered by significant technical variations, including differences in chemotherapeutic agents, dosages, temperatures, duration of perfusion, and delivery methods [1]. These variations have led to inconsistent outcomes across different centers and studies, highlighting the urgent need for standardized protocols. Furthermore, merging data or comparison of outcomes between centers is problematic due this heterogeneity of treatments also undermining credibility of the method.

The PSOGI (Peritoneal Surface Oncology Group International) and RENAPE (French Network for Rare Peritoneal Malignancies) recognized these challenges and aimed to address the

inconsistencies by providing clear consensual guidelines based on the best available evidence and expert consensus. By doing so, it sought to harmonize practices worldwide and enhance the efficacy and safety of HIPEC treatments, fostering the collaboration of Peritoneal Surface Oncology experts. This effort is particularly crucial for rare and complex peritoneal malignancies, where optimized treatment protocols can significantly impact patient outcomes [2–7].

2 | Methodology

The consensus process involved a meticulous evaluation of existing evidence through the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.

The meta-analysis evaluated randomized controlled trials (RCTs) and nonrandomized controlled trials (NRCTs) comparing surgery combined with HIPEC versus standard surgical management. Studies included clearly defined HIPEC interventions in cytoreductive surgery (CRS), excluding those with vague descriptions or alternative chemotherapy methods. The analysis aimed to assess overall survival (OS) and severe postoperative morbidity, with primary outcomes including survival rates by type of drug and extent of carcinomatosis. The statistical analysis used a random-effects model to handle heterogeneity, employing pooled odds ratios (OR) or hazard ratios (HR), with the R version 4.1.0 (May 18, 2021) software, with the "metafor" package for calculations. Heterogeneity was assessed using Cochran's Q value and I^2 inconsistency test, with significance set at a p value of 0.05. This comprehensive approach highlighted the survival benefits and morbidity impacts of HIPEC, despite limitations due to study bias and variability.

This rigorous approach ensured a thorough assessment of the certainty of evidence to establish the strength of recommendations. The consensus was derived using a two-round Delphi process involving more than 140 international experts, with at least a 71% participation rate in both rounds. As most of the clinical questions raised during the consensus were expected to generate convergent consensus based on evidence, a separate section surveying expert opinion was conducted, asking them the preferable option for clinical routine use and future research. This method ensured broad representation and validation of opinions, leading to a consensus on most clinical questions related to HIPEC regimens [6].

3 | Pseudomyxoma Peritonei (PMP)

3.1 | Literature Review

From 268 articles, 6 noncomparative cohort studies, 2 PMP treatment consensus guidelines, and 2 comparative studies (1 RCT and 1 NRCT) were identified. Various HIPEC drug regimens for PMP were examined, but head-to-head comparative studies are scarce. The only RCT by Levine et al. [8] compared HIPEC using Oxaliplatin (200 mg/m^2) with mitomycin C (MMC) (40 mg, ASPSM regimen) in PMP patients undergoing CRS, finding similar outcomes but better quality of life with Oxaliplatin. The study's evidence certainty was rated low due to randomization concerns and insufficient power for survival analysis. The PSOGI registry study, using propensity score matching, found significant OS benefits with CRS/HIPEC regimens of CDDP + MMC and Ox + 5FU, though high-dose MMC increased severe morbidity [9].

3.2 | Recommendations on HIPEC in PMP

Eighty-four percent of the panelists strongly recommended using HIPEC following CRS for PMP to enhance treatment effectiveness and improve patient outcomes. Taking together with the data results of the technological section, the recommended PMP regimens include cisplatin (CDDP 75 mg/m^2) and MMC (12.5 mg/m^2). Additionally, the high-dose MMC regimen (35 mg/m^2) received solid support, with 89% of the panelists favoring its use, despite its unfavorable safety profile [3].

4 | Peritoneal Mesothelioma

4.1 | Literature Review

The systematic review, encompassing 28 studies, included 4 retrospective comparisons of HIPEC regimens, 18 cohort outcomes, 1 meta-analysis, and 5 guidelines [5, 10–13]. Six primary HIPEC protocols were frequently used: cisplatin, MMC, carboplatin, oxaliplatin alone, and combinations of cisplatin–doxorubicin and cisplatin–MMC [14–17]. The literature was largely heterogeneous, retrospective, and noncomparative, resulting in a low certainty of evidence. This variability stemmed from the aggressive and rare nature of diffuse malignant peritoneal mesothelioma (DMPM) and the inclusion of low-grade peritoneal mesothelioma cases. Notably, cisplatin was a cornerstone in HIPEC regimens for mesothelioma, particularly effective when paired with intravenous sodium thiosulfate (STS) to prevent renal toxicity. The combination of cisplatin and doxorubicin emerged as the most effective, offering the best long-term OS with manageable toxicity.

4.2 | Recommendations on HIPEC in Peritoneal Metastasis (PM)

HIPEC following complete CRS received strong support from 88% of voters, with 61.2% indicating no need for comparative studies with CRS alone. Bi-drug regimens were favored over mono-drug ones, with a general preference for cisplatin. The survey confirmed the combination of cisplatin 50 mg/m^2 and doxorubicin 15 mg/m^2 as the recommended regimen [5].

5 | Epithelial Ovarian Cancer

5.1 | Literature Review

The review synthesized data from various studies to address the significant heterogeneity in HIPEC protocols, focusing on drug regimens, perfusion durations, and temperatures. One of the

key studies examined was the OVHIPEC-1 trial [18]. It demonstrated a clear survival benefit when cisplatin-based HIPEC was added to interval CRS, establishing it as the most favored regimen among experts.

The review highlighted the pharmacokinetic advantages and thermal enhancement properties of cisplatin, making it the preferred agent for HIPEC. Despite cisplatin's efficacy, the review also considered other drugs, such as Carboplatin [19], doxorubicin [20], and oxaliplatin [21]. While Carboplatin has a potentially favorable pharmacokinetic profile, it lacks robust clinical trial evidence supporting its use over cisplatin. Doxorubicin and oxaliplatin were noted for their pharmacokinetic profiles and synergistic effects with hyperthermia, though concerns about toxicity and efficacy limited their recommendations.

Nephroprotection emerged as a crucial aspect of the HIPEC procedure due to the nephrotoxic potential of cisplatin. The literature review pointed to the use of STS to prevent renal toxicity, supported by studies showing its effectiveness in reducing cisplatin-induced nephrotoxicity—this recommendation aimed to standardize perioperative care and enhance the safety profile of HIPEC [22].

The review highlighted the lack of strong evidence for using HIPEC in primary or recurrent EOC settings, emphasizing the need for further RCTs to validate its efficacy in these contexts. The heterogeneity in existing data, including variations in drug regimens, perfusion techniques, and patient selection criteria, underscored the necessity for standardized protocols. The consensus identified critical areas for future research, such as comparing different HIPEC regimens and determining the optimal duration and temperature for HIPEC procedures [2].

5.2 | Preferred Chemotherapeutic Agents

Cisplatin was the most preferred drug either alone or in combination, for performing HIPEC and the OVHIPEC-1 regimen was the most preferred regimen. The panel recommended performing HIPEC for a minimum of 60 min with the minimum intra-abdominal temperature being 41°C; HIPEC should be offered to patients with BRCA mutations and those scheduled to receive maintenance bevacizumab when indicated. Progression-free and OS were both considered suitable endpoints for clinical trials on HIPEC [2].

6 | Colorectal Peritoneal Metastases

6.1 | Literature Review

The PRODIGE 7 trial found no survival benefits when adding high-dose, short-duration oxaliplatin-based HIPEC to complete CRS, with severe complications higher in the HIPEC arm (OR 1.99). Only patients with an intermediate Peritoneal Cancer Index (11–15) showed a survival benefit, while both groups exhibited unexpectedly high OS, underscoring the importance of high-quality CRS and systemic chemotherapy [23]. In colorectal cancer (CRC), pooled analysis of three observational studies (225 patients) demonstrated that MMC-based HIPEC added to CRS led to better survival without increased complications [24–26]. Various MMC combinations were used, and high median OS was noted in groups receiving systemic treatment and CRS, similar to HIPEC, with no higher severe complication rate. Eleven studies comparing MMC-based HIPEC with oxaliplatin (OX)-based regimens showed no survival benefit between the regimens, although OX-based HIPEC had more complications [27]. High-dose oxaliplatin (350–460 mg/m^2) compared to low-dose MMC (10–15 mg/m^2) in three studies showed significantly better OS with high-dose OX HIPEC and no difference in morbidity [28–30]. Adding irinotecan to high-dose OX led to more severe complications without survival advantage, according to Quenet et al. Four studies comparing high-dose OX with high-dose MMC found no survival difference but more severe complications with OX [31]. One study comparing low-dose OX HIPEC (200 mg, 120 min) with high-dose MMC (40 mg) showed no survival difference but more severe complications in OX-treated patients [32]. Finally, two studies examined outcomes of repeat CRS and HIPEC for isolated recurrence compared to palliative systemic treatment, while other studies reported follow-up after the second CRS and HIPEC without control groups.

6.2 | Recommendations on HIPEC in Peritoneal Metastases From Colorectal Cancer (PM-CRC)

There was strong negative consensus regarding the short-duration, high-dose OX protocol (55.7%), while a weak positive consensus (53.8%–64.3%) supported MMC-based HIPEC, with the Dutch protocol (35 mg/m^2, 90 min, three fractions) being the preferred choice for both primary cytoreduction and recurrence. Determining the role of HIPEC after CRS was deemed the most critical research question, with 85.7% of panelists considering it essential. Additionally, over 90% of experts recommended performing HIPEC after both primary and secondary CRS for recurrence occurring more than 1 year after the initial surgery [4].

7 | Gastric Cancer

7.1 | Literature Review

The use of HIPEC in gastric cancer with a high risk of peritoneal metastasis (PM) was explored by the panelists. For patients undergoing radical gastrectomy for locally advanced gastric cancer, 17 studies (7 RCTs and 10 NRCTs) were reviewed, revealing a statistically significant survival advantage for HIPEC (polled HR 0.52; 95% CI 0.43–0.63, $p < 0.0001$) without increased severe postoperative morbidity (polled HR 0.89; 95% CI 0.46–1.72, $p > 0.05$) [33–49]. The evidence of the studies was downgraded due to bias and inconsistency. MMC and cisplatin were the most common drugs used, alone or in combination with others like etoposide.

Regarding the curative use of HIPEC compared to CRS for treating gastric cancer with PM, one RCT and eight NRCTs

showed a survival benefit favoring HIPEC (polled HR 0.47; 95% CI 0.37–0.61, $p < 0.0001$) without increased postoperative morbidity. The evidence from these studies was considered low due to the high risk of bias and inconsistency [36, 44, 50–56].

For prophylactic or curative intent using MMC-based HIPEC, four RCTs and three NRCTs indicated a significant survival advantage (polled HR 0.58; 95% CI 0.45–0.75, $p < 0.0001$), with no significant differences in severe postoperative morbidity (polled HR 0.75; 95% CI 0.04–13.00, $p > 0.05$). Similarly, HIPEC using MMC and CDDP after surgery showed a survival benefit (polled HR 0.39; 95% CI 0.31–0.49, $p < 0.0001$) without increased morbidity (polled HR 1.51; 95% CI 0.47–4.82, $p > 0.05$). For HIPEC using CDDP alone, the data from one RCT and one NRCT did not show a survival advantage (polled HR 0.504; 95% CI 0.237–1.0611, $p > 0.05$) but indicated lower postoperative morbidity. The combination of MMC, CDDP, and etoposide showed a survival benefit (HR 0.63; 95% CI 0.44–0.90, $p < 0.0001$) without increased morbidity. Finally, a single RCT on repetitive postoperative HIPEC using oxaliplatin and 5-FU showed significant survival benefits (polled HR 0.38; 95% CI 0.15–0.97, $p < 0.05$) with no difference in severe morbidity. Overall, these findings suggest HIPEC provides a survival advantage in high-risk gastric cancer patients, though further high-quality research is needed to solidify these conclusions [57].

7.2 | Recommendations on HIPEC in PM-GC

For gastric cancer, the application of HIPEC following CRS was recommended by the expert panel in both preventive and curative settings to improve survival and quality of life through combined modality treatment. Regarding the specific regimen recommendation, the combination of cisplatin 75 mg/m^2 and MMC 12.5 mg/m^2 was chosen as the most advisable [57].

8 | Technological Considerations

The consensus favored the closed HIPEC system due to more stable intra-abdominal temperatures and reduced contamination risk, supported by 82.3% of the panel. Despite limited data, both open and closed techniques showed similar outcomes, leaving the choice to the surgeon's discretion. The role of hyperthermia in HIPEC was strongly endorsed, with optimal temperatures debated between 41°–42°C and 42°–43°C. There was consensus on the necessity for further research into the biological mechanisms of thermal enhancement. Regarding the timing of anastomoses, performing them before HIPEC was acceptable to 66.7% of experts, despite concerns about tissue edema post-HIPEC. The use of four inflow catheters was recommended to ensure temperature homogeneity. Additionally, at least three temperature probes were advised to measure heat distribution accurately. Drug dosing should be based on mg/m^2, with perfusate volumes at 2 L/m^2. Prophylactic drains post-HIPEC were recommended to manage fluid loss and contamination. Extensive lavage with normal saline post-CRS was endorsed to lower the peritoneal tumor burden. Safety measures, including staff education and protective equipment, were deemed essential. A 35 mg/m^2 MMC-based HIPEC regimen was recommended, with a target temperature of 41°–42°C. For cisplatin-based regimens, a 100 mg/m^2 dose over 90 min at 41°–42°C was advised, with STS to mitigate renal toxicity. The preferred oxaliplatin regimen was 200 mg/m^2, with 5-FU recommended as an adjunct and a temperature of 41°–42°C. These recommendations aim to standardize HIPEC protocols to improve patient outcomes and reduce complications, with further research essential to validate these practices [7].

9 | Discussion

HIPEC was proven to be beneficial by RCTs in the following PSM settings: after neoadjuvant systemic chemotherapy as secondary cytoreduction in advanced epithelial ovarian cancer [18] after cytoreduction of platinum-sensitive epithelial ovarian cancer [58] as adjuvant therapy after resection of T4 primary CRC with preventive intention [59]. Moreover, CRS and HIPEC are considered the standard of care for malignant peritoneal mesothelioma and PMP [60, 61].

Over the past two decades, the role of HIPEC following CRS has been critically examined in patients with PM-CRC. The PRODIGE-7 trial's findings led to a consensus recommendation to discontinue the high-dose, short-duration Oxaliplatin-based HIPEC regimen due to its ineffectiveness and associated higher morbidity risks, including increased bleeding. In contrast, MMC-based HIPEC regimens have gained favor, albeit with limited evidence supporting their superiority in terms of survival outcomes. The consensus confirms an already trend of a shift in preference toward MMC-based HIPEC, despite the lack of high-quality data indicating significantly better outcomes.

The failure of the Oxaliplatin-based HIPEC in the PRODIGE-7 trial should not lead to the complete dismissal of Oxaliplatin as a viable drug for HIPEC. Instead, the trial's methodology, particularly the short duration of perfusion, may have contributed to its ineffectiveness [23]. The trial was neither designed nor adequately powered to identify a potentially clinically significant benefit in controlling locoregional disease. Moreover, preclinical studies suggest that longer durations of Oxaliplatin-based HIPEC could enhance its cytotoxic effects, prompting ongoing research into alternative regimens with extended perfusion times [62]. This area of investigation remains a crucial pathway for future research.

In the realm of preventive strategies, “prophylactic” HIPEC has been investigated as a means of preventing peritoneal metastases in high-risk CRC patients. Despite the flawed Oxaliplatin-based regimens used in previous trials, the consensus still considers this approach a vital research priority, particularly with MMC-based HIPEC regimens. In fact, a trial that was not available during the consensus process was recently published, demonstrating through randomization that HIPEC with MMC can provide better locoregional control in CRC T4 cases with a high risk of metachronous peritoneal recurrence [59].

In the context of PMP, the consensus strongly recommends the use of HIPEC following CRS, with a preference for the CDDP/MMC and high-dose MMC regimens. This recommendation is grounded in the perceived balance between benefits and risks,

TABLE 1 | Summary of HIPEC regimens recommended for different clinical scenarios.

Primary site [reference no]	Clinical/trial setting	First option	Second option
Colorectal cancer [4]	HIPEC regimen for patients with colorectal peritoneal metastases who were not treated with systemic therapy in the 6 months before CRS and HIPEC	MMC high dose (35 mg/m^2)	Cisplatin (CDDP 75 mg/m^2) and mitomycin-C (MMC 12.5 mg/m^2)*
	HIPEC regimen for patients with colorectal peritoneal metastases who were treated with oxaliplatin-containing systemic therapy (either in adjuvant or neo-adjuvant setting) in the 6 months before CRS and HIPEC	MMC high dose (35 mg/m^2)	Cisplatin (CDDP 75 mg/m^2) and mitomycin-C (MMC 12.5 mg/m^2)*
PMP [3]	HIPEC regimen for a trial comparing CRS + HIPEC versus CRS alone	Cisplatin (CDDP 75 mg/m^2) and mitomycin-C (MMC 12.5 mg/m^2)*	Dutch High Dose Mitomycin C (35 mg/m^2)
	HIPEC regimen for a trial comparing two HIPEC regimens	Cisplatin (CDDP 75 mg/m^2) and mitomycin-C (MMC 12.5 mg/m^2)*	Dutch High Dose Mitomycin C (35 mg/m^2)
Peritoneal mesothelioma [5]	HIPEC regimen for HIPEC after complete cytoreductive surgery	Cisplatin 50 mg/m^2 + doxorubicin 15 mg/m^2	Cisplatin 100 mg/m^2 + doxorubicin 15 mg/m^2
	HIPEC regimen for HIPEC after complete iterative cytoreductive surgery	Cisplatin 100 mg/m^2 + doxorubicin 15 mg/m^2	Cisplatin 50 mg/m^2 + doxorubicin 15 mg/m^2
Epithelial ovarian cancer [2]	HIPEC regimen for advanced epithelial ovarian cancer (HIPEC was recommended only after interval CRS in routine practice; after primary CRS, it was recommended only in the setting of a clinical trial)	OVHIPEC-1 regimen Cisplatin 100 mg/m^2 for 90 min with triple dosing and use of sodium thiosulphate	CHIPASTIN regimen Cisplatin 75 mg/m^2 for 60 min
	HIPEC regimen for recurrent epithelial ovarian cancer (HIPEC for recurrent disease was recommended only in the setting of a clinical trial; the CHIPOR trial results were not available when the consensus was carried out)	OVHIPEC-1 regimen Cisplatin 100 mg/m^2 for 90 min with triple dosing and use of sodium thiosulphate	CHIPASTIN regimen Cisplatin 75 mg/m^2 for 60 min
	HIPEC regimen for mucinous epithelial ovarian cancer	Any Cisplatin (single-agent) based regimen	Any Cisplatin and doxorubicin combination
	HIPEC regimen for evaluation in clinical trials	OVHIPEC-1 regimen Cisplatin 100 mg/m^2 for 90 min with triple dosing and use of sodium thiosulphate	CHIPASTIN regimen Cisplatin 75 mg/m^2 for 60 min
Gastric cancer [unpublished results]	HIPEC regimen for prophylactic HIPEC in locally advanced gastric cancer	Cisplatin (CDDP 75 mg/m^2) and mitomycin-C (MMC 12.5 mg/m^2)*	Cisplatin 50 mg/m^2 + doxorubicin 15 mg/m^2*
	HIPEC regimen for curative treatment of gastric peritoneal metastases with cytoreductive surgery and HIPEC	Cisplatin (CDDP 75 mg/m^2) and mitomycin-C (MMC 12.5 mg/m^2)*	Cisplatin alone 50 mg/m^2 or 50 mg/L of the perfusate for 60 min

Note: Only the first two choices are listed here. The complete results are available in the respective manuscripts on each subject. Taken together with the data from the technological section of the consensus [7].

despite the low certainty of available evidence. An intriguing aspect of HIPEC's efficacy, highlighted by the PMP PSOGI registry study, is the unexpected data that a survival advantage may be observed even in cases of nonoptimal cytoreduction. This finding warrants further investigation.

Regarding patients with gastric cancer, although pooled data suggest a potential advantage of performing HIPEC in both prophylactic and curative settings after surgery, caution is advisable in delivering conclusions due to important limitations of the available evidence and due to the significant evolution in medical treatment for advanced and metastatic gastric cancer observed over the last decades. The external validity of such results is limited as most of the studies were conducted in a period in which none of the current modern perioperative systemic therapies were available [63].

For patients with DMPM, the consensus recommends the combination of cisplatin and doxorubicin as the first-line HIPEC protocol after complete CRS. DMPM, being a primary peritoneal disease that rarely spreads outside the peritoneal cavity, has long been treated with intraperitoneal chemotherapy, and HIPEC has become the standard of care in eligible patients. The consensus reflects a pragmatic approach, favoring this combination regimen despite the limited and low-level evidence available. This approach aims to standardize treatment for this rare disease while awaiting higher-level evidence and innovative strategies such as immunotherapy of other local-regional approaches [64, 65].

Technological aspects of HIPEC, particularly the lack of standardization regarding drug choice, dose, duration, and other variables, present a significant challenge. Currently, there are over 60 different HIPEC schedules used in the treatment of PM-CRC, reflecting the diverse and often empirical nature of the field's development. Many of these schedules were introduced into clinical practice without the rigorous preclinical and clinical testing typically required for new oncological treatments. This empirical approach may have resulted in regimens with acceptable morbidity but potentially suboptimal therapeutic efficacy due to non-optimized drug dosages.

The optimization of HIPEC regimens through traditional scientific pathways, involving extensive preclinical studies followed by phased clinical trials, poses significant challenges due to the complexity and resource-intensive nature of such trials. Moreover, the inherent variability in HIPEC techniques adds to the difficulty of conducting standardized studies. Despite these challenges, the recent surge in preclinical research, spurred by the findings of the PRODIGE-7 trial, has shifted focus toward understanding the underlying biology of peritoneal metastases, in particular to antitumor immunity in tumor microenvironment [66–69]. New preclinical platforms, such as tumor-derived organoids, have emerged, offering a more accurate representation of in vivo disease conditions compared to traditional 2D cell lines. These organoids also enable the testing of chemosensitivity, which can help guide treatment decisions. This research, coupled with advances in molecular profiling and personalized medicine, holds promise for the future optimization and standardization of HIPEC.

TABLE 2 | Preferred regimen for each drug (from [7]).

Drug	Dose	Fractions	Duration	Temperature	Carrier solution
Mitomycin C	35 mg/m^2	3: 50% at the beginning, 25% at 30 min, and 25% at 60 min	90 min	41°–42°C	—
Cisplatin	100 mg/m^2 In combination with other drugs Cisplatin 75 mg/m^2 + MMC 12.5 mg/m^2 Cisplatin 50 mg/m^2 + Doxorubicin 15 mg/m^2	3: 50% at the beginning, 25% at 30 min, and 25% at 60 min	90 min	41°–42°C	0.9% Saline
Oxaliplatin	200 mgG/m^2 With 5-FU (preferred)	Single fraction	90min (consensus not reached)	41°–42°C	5% Dextrose (consensus not reached)
Paclitaxel	175 mg/m^2	Single fraction	90 min	41°–42°C	0.9% Saline

In conclusion, while complete CRS remains the cornerstone of treatment for PM-CRC, HIPEC continues to be a valuable adjunctive therapy. For PMP, DMPM, PM-CRC, EOC, and PM-GC, the consensus supports the use of HIPEC following CRS, with specific regimens recommended for clinical practice and future research (Tables 1 and 2). Despite the current limitations in evidence, these recommendations represent a significant step forward in standardizing HIPEC and set the stage for further clinical and translational research to optimize this complex and promising treatment modality.

10 | Conclusion

The PSOGI/RENAPE consensus provides a comprehensive framework for applying HIPEC in the treatment of various peritoneal malignancies. By standardizing treatment protocols and identifying key research priorities, the consensus aimed to improve patient outcomes and advance the field of peritoneal surface oncology that can be done not only by clinical trials but also by multicenter evaluation of these treatments through international registries. Detailed recommendations for different disease settings underscore the tailored approach required to manage these complex conditions effectively.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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